

REPORT NUMBER 980
Workshop on
DETECTION AND MEASUREMENT
OF PULMONARY OXYGEN TOXICITY
held at

Naval Submarine Medical Research Laboratory
Naval Submarine Base New London
Groton, Connecticut

Chairman: C. J. Lambertsen
Editor: R. G. Eckenhoff
Co-ordinators: J. W. Parker
R. G. Eckenhoff

Dates - 27 and 28 October
1981

Released by:

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Commanding Officer
Naval Submarine Medical Research Laboratory
28 January 1983

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NSMRL Report No. 980

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SUMMARY PAGE

THE PROBLEM

Controversy and contradiction exist in the various reported methodologies directed at the characterization of pulmonary oxygen toxicity. Because the study of human pulmonary oxygen toxicity is a major component of ongoing research activities at this laboratory, several military and civilian scientists with expertise in various aspects of pulmonary physiology were assembled to discuss the disease and its detection.

FINDINGS

Recommendations and limitations of methodologies ranging from conventional spirometry to nuclear magnetic resonance were obtained.

APPLICATION

Subsequent to this meeting, NSMRL scientists assembled, tested and applied an investigational package which included many of the recommendations from this workshop to experiments in which 15 human subjects were exposed to air at 5 atmospheres absolute for 48 hours.

ADMINISTRATIVE INFORMATION

This workshop was supported by the American Institute for Biological Sciences under contract No. N0014-75-C-0348 and Naval Medical Research and Development Command Work Unit No1 M0099.01A-0006.

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ABSTRACT

As part of this laboratory's continuing research in shallow air saturation diving in support of the Navy's submarine rescue capability, several military and civilian scientists met for two days to discuss pulmonary oxygen toxicity and the various methods of its detection and quantification. The pathogenesis, biochemistry, and characteristics of the disease in both animals and humans were reviewed and discussed at length. Methods ranging from conventional spirometry to nuclear magnetic resonance to expired gas chemoluminescence were presented. Specific recommendations and limitations of the techniques were obtained concerning the application of these techniques to humans in a hyperbaric environment. The need for additional data concerning the progression and recovery from pulmonary oxygen toxicity in both man and animals was apparent during this workshop.

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FOREWORD

The need for this workshop was realized when planning for a series of experiments where human subjects were to be exposed to hyperbaric air at five atmospheres absolute for prolonged periods of time. Signs and symptoms of pulmonary oxygen toxicity were expected to develop in these subjects and an investigational package to accurately document the onset and progression was sought. Tests chosen for use in human studies must be sensitive and reliable, due to the usually limited number of subjects, and so that extrapolation to the point of incapacitation or death can be made. From past experience at this and other laboratories, conventional spirometry as an index of pulmonary oxygen toxicity was not entirely satisfactory, both because of the effort dependent nature of the maneuvers, and the lack of correlation with symptoms in some subjects. Therefore, other indices were desired.

The literature abounds with methodology directed at the characterization of pulmonary oxygen toxicity. Much of this work is in

animal models and would be inappropriate for application to humans in any setting. Of the techniques which have been used in humans, much contradictory and confusing information exists.

Herein lies the basis for this workshop. Can the knowledge gained in the past decade be applied to the characterization of pulmonary oxygen toxicity in humans? Are there indices which correlate more closely with the actual pathogenesis at the cellular or membrane level than such gross, indirect and unexplained methods as forced expiratory spirometry? Which of these would be feasible for studies at this laboratory? These and other questions were addressed by the participants of this workshop. What follows are summaries of the individual presentations and subsequent discussions. Then, in order to obtain specific recommendations for our investigations, and the advantages and limitations of the discussed techniques, a working session was included, the summary of which appears at the end of this report.

OPENING REMARKS

D. R. Knight

The Navy currently relies on the Deep Submergence Rescue Vehicle (DSRV) for rescue of submarine crews stranded in deep water. The problem with the DSRV is that crewmembers must survive for 48-72 hours in the disabled submarine, while awaiting arrival of the DSRV from its home port. One of the environmental factors which may threaten the welfare of the waiting crewmembers is pressurization of their compartment's air. When this happens, the crew members become predisposed to narcosis, decompression sickness, and oxygen toxicity.

The Naval Submarine Medical Research Laboratory, NSMRL, has been productively investigating the health aspects of compartment pressurization for the last decade. Nitrogen narcosis was found to be tolerable at pressures as great as 7 ATA, despite measurable decrements of behavior and task performance. Therefore, a plan was required for prevention of decompression sickness following rescue of the survivors from submarines pressurized to 7 ATA. NSMRL developed decompression tables for emergency decompression of humans saturated with hyperbaric nitrogen. Then the question arose as to whether or not diving ships' air systems needed to be modified to provide mixtures of nitrogen-oxygen gas for submarine rescue. Dr. Lambertsen's theoretical

and experimental work on isobaric counter-diffusion of inert gases was applied by NSMRL to determine the advisability of using helium-oxygen gas mixtures for decompressing humans saturated with hyperbaric nitrogen. Symptoms of decompression sickness occurred when the hyperbaric environment was isobarically changed from nitrogen-oxygen to helium-oxygen gas mixtures, demonstrating the necessity for decompressing survivors of prolonged compressed air exposures with nitrogen-oxygen media.

The Navy's current question is whether or not men can safely tolerate 48 hours of residence in air pressurized to 5 atmospheres absolute. In a recent set of experiments, conventional tests of pulmonary function and clinical welfare were used to judge the presence or absence of pulmonary oxygen toxicity in subjects exposed to hyperbaric air. Because more sensitive indicators of pulmonary oxygen toxicity may exist elsewhere, the investigators at NSMRL want to apply current research technology to achieve early and accurate quantification of pulmonary oxygen toxicity in human volunteers. The goal of this workshop is to improve NSMRL's technical and scientific approach to the study of pulmonary oxygen toxicity in humans exposed to compressed air.

PULMONARY OXYGEN TOXICITY AND SUBMARINE RESCUE

R. G. Eckenhoff

The research in which we are presently involved is primarily in support of the U.S. Navy submarine rescue capability. The basis for the connection of saturation diving experiments and submarine rescue is simply that; a) any casualty resulting in the sinking of a submarine has a high probability of causing compression of the submarine's atmosphere, and b) present U.S. Navy submarine rescue vehicles cannot respond for at least 48 hours. Thus the submarine's crew will be saturated on air at the submarine's internal--pressure anywhere from 1 ATA to ambient. However, the has been designed to effect a rescue at internal pressures only up to 5 ATA, as a greater degree of pressurization is believed to result in unrescuable conditions.

Air at 5 ATA contains about 800 mmHg of oxygen or about 1 ATA. Exposure to this atmosphere for periods of 36-48 hours will result in signs and symptoms of pulmonary oxygen toxicity which may seriously affect the survival and handling of crewmembers after rescue. Normobaric 100% oxygen studies ($pO_2=1.00$ ATA) have confirmed this, but a parallel to the situation at 5 ATA air cannot be assumed as there is evidence showing that diluted oxygen (equivalent partial pressures) is generally tolerated better, both in humans and animals. The mechanism is unclear; it may be related to the role of atelectasis, a ventilatory or diffusion effect of the relatively denser gas implied by the diluted oxygen mixture, or a narcotic/CNS effect of the elevated inert gas partial pressure.

Fundamentally, then, we are interested in determining the characteristics and rate of development of pulmonary oxygen toxicity in humans

exposed to 5 ATA air, so that the condition of submarine survivors can be predicted. This information may allow a) improved procedures/equipment in submarine rescue and b) optimal handling of survivors after rescue.

Studies at this laboratory to date have shown that:

a) Humans can tolerate hyperbaric air at 2.8 ATA ($pO_2=0.60$ ATA) for periods of at least a week with only minimal signs and symptoms consistent with pulmonary oxygen toxicity.

b) A pO_2 of about 0.60 ATA is probably very close to the safe tolerable limit for human exposures.

c) Humans can tolerate 24 hours exposure to 5 ATA air (800 mmHg) with a subsequent air decompression, and demonstrate only moderate symptoms and mild decrements in the vital capacity.

More detail concerning these experiments will be addressed by Mr. Dougherty. The continuation of these studies has the goal of examining the tolerance of a 48 hour exposure to 5 ATA air. The next series, scheduled to begin in fall of 1982, will approach this exposure. The preliminary design of this 'dive' includes a 48 hour stay at 5 ATA breathing normoxic nitrogen ($pO_2=0.30$ ATA) prior to the isobaric switch to air. The air exposure will continue for the remaining time at 5 ATA (at least 30 hours) and through decompression. This design is preliminary, and is open to comments and discussion.

Although there is no question that vital capacity decrements are observed in early stages of pulmonary oxygen

toxicity, its sensitivity and meaning are open to question. The mechanism of the vital capacity decrement remains unknown. There is even disagreement on how best to perform the vital capacity and associated pulmonary mechanics maneuvers. For these reasons, we are interested in pursuing additional methodology for the detection and quantification of pulmonary oxygen toxicity in humans. Since human studies cannot be carried to the degree of irreversibility, it is important that these methods be reliable and sensitive in detecting and following early pulmonary oxygen toxicity, so that extrapolation and prediction about the point of incapacitation or death, can be

made. Reports abound concerning the applicability of: lung water determinations, pulmonary lymph flow, permeability changes, biochemical markers (serotonin, prostaglandins, angiotensin converting enzyme, antioxidant enzymes, fibronectin, etc.) and gas exchange in pulmonary oxygen toxicity. Are these techniques applicable to humans in a hyperbaric chamber? Which have the most potential? It is for this sort of question that the present workshop was initiated. Additional methodology will not only enable the experiments to better answer the operational questions, but also to provide more insight into the human tolerance of oxygen.

PULMONARY OXYGEN TOXICITY IN HUMANS EXPOSED TO HYPERBARIC AIR

J. H. Dougherty

The following is a summary of pulmonary function data obtained during air saturation (AIRSAT) experiments 1, 2 and 3. Briefly, AIRSAT 1 and 2 were week long exposures to a storage depth of 60 fswg breathing air, with air excursions to 100 fswg for 8 hours in the former, and 150 fswg for 2 hours in the latter. The storage depth for AIRSAT 3 was 132 fswg with an initial period of normoxic storage and air excursions to 200 fswg, and then a 24 hour exposure to air at the same storage depth with a subsequent air decompression. Thirty-four subjects were involved in these three experiments, and no subjects were used twice.

Forced expiratory spirometry was performed using a Med-Science Electronics wedge spirometer, a pulmodigitizer and an x-y oscilloscope for monitoring and coaxing. All tests were performed at least in duplicate, the higher value being recorded. Other lung volumes and diffusing capacity were obtained in the pre and post dive periods only.

Significant symptoms of chest discomfort, retrosternal irritation and cough were found in about 30% of AIRSAT 1 subjects, 35% of AIRSAT 2 subjects and 90% of AISAT 3 subjects. Significant decrements (greater than 2 SD of their control values) in the forced vital capacity (FVC) occurred in about 15% of AIRSAT 1 subjects, 30% of AIRSAT 2 subjects and 50% of AIRSAT 3 subjects.

The mean maximal decrement in FVC was approximately 2.5% of control in AIRSAT 1, 2.0% in AIRSAT 2 and 6% in AIRSAT 3. Individual variability was noteworthy, with some subjects showing greater than a 20% decrement, and others virtually

none. The symptoms generally, but not always, preceded the changes in the FVC, and correlated in degree. Although no correlation between age and the FVC decrement was observed, the smokers as a group had a larger mean FVC decrement than the nonsmoking group.

Besides the expected depth related changes in flow rates, no significant change in the forced expired volume in one second, forced expired volume in two seconds, peak expiratory flow rate, or peak inspiratory flow rate was noted.

The mean post dive single breath diffusing capacity was lower than that in the predive period in all cases, but only showed statistical significance in AIRSAT 3. The maximal drop was in the third postdive day, with almost complete recovery by the fifth postdive day.

Some preliminary measurements of the inspiratory/expiratory time ratio during quiet breathing were taken. No significant changes were noted, but the sample size was small.

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DISCUSSION

Several group members asked for clarification of the submarine rescue procedures and capabilities. The response can be summarized as follows:

a) Only two DSRVs exist, and both are stationed in San Diego. They can be transported by either land, sea or air, but the complexity of the transportation operation is such that a 48 hour response time may be optimistic.

b) The DSRV is a transfer vessel, capable of removing about one fifth of the submarine crew at a time. Therefore, several trips may be required.

c) The DSRV can be pressurized to 5 ATA, but cannot perform the necessary prolonged saturation decompression. Therefore, the DSRV occupants must be transferred to a facility for decompression (Deck Decompression Chamber - DDC).

d) The distressed submarine crewmembers would be unable to breathe normoxic nitrogen/oxygen while on board the submarine, or while in the DDC, but could while on board the DSRV. However, the DDC could be 'rigged' so that the

occupants would breathe down the O₂ level--which could then be maintained at this lower level by the oxygen make-up system.

Several comments concerning the data presented by Mr. Dougherty were made;

a) Protocols are complex. It is difficult to interpret what is going on at any one point due to the changes preceding it.

b) In a previously healthy subject a 25% decrement in vital capacity may have very little meaning, so clinical significance should be defined carefully.

c) Data must be considered in terms of both populations and individuals.

Dr. Eckenhoff asked the group to comment on two aspects of the experimental design of AIRSAT 4; a) the exposure duration at 5 ATA air, and b) the period of normoxic nitrogen oxygen (nitrox) at 5 ATA prior to the air exposure. The ensuing discussion resulted in the following recommendations:

1) The members agreed that an exposure duration of at least 48 hours, rather than the 30 hours planned, should be the next step. Information will be obtained more rapidly, and the subject's safety will not be compromised due to the ease of switching back to a normoxic atmosphere when a predetermined level of signs/symptoms has been reached in any subject.

2) Agreement was not immediately forthcoming with point b). While some group members maintained that a 48 hour period was necessary to obtain adequate control information for the subsequent air exposure, others claimed that it would have an unknown effect on the subsequent tolerance of the air exposure making interpretation difficult. No

concensus was reached, but a reasonable compromise put forth by Drs. Menkes and Clark was to use a shorter period of normoxic nitrox (12 hours or less) which

would allow measurement of the acute effects of hyperbaria alone, and introduce minimal contamination of the air exposure data.

THE PATHOGENESIS AND BIOCHEMISTRY OF PULMONARY OXYGEN TOXICITY

A. B. Fisher

Pulmonary Oxygen Toxicity can be divided into four different syndromes:

1) Absorption atelectasis.

Important with 100% oxygen, but less so with diluted mixtures (independent of the pO_2). May cause vital capacity to decrease, and cause arterial desaturation.

2) Tracheobronchitis.

Consists of substernal discomfort and cough. Decreased tracheobronchial clearance may be first manifestation of this syndrome and pulmonary oxygen toxicity in general. This syndrome is probably not important by itself, but is a harbinger of more serious manifestations and may lead to secondary effects such as increased susceptibility to infection.

3) Adult Respiratory Distress Syndrome (ARDS).

Consists of progressive dyspnea, acidosis and death. Noncardiogenic pulmonary edema is predominant finding in this terminal, possibly irreversible phase of oxygen toxicity.

4) Bronchopulmonary dysplasia.

Characterized by progressive restrictive pulmonary problems with time. May be caused by chronic exposure to an elevated pO_2 insufficient to cause ARDS. Consists primarily of fibrosis and cellular proliferation.

The ARDS syndrome will be dealt with for the remainder of this presentation. In the progression of pulmonary oxygen toxicity, the pulmonary endothelial cell is first to change, with subsequent swelling of the

interstitium. Type I alveolar cells are next affected, followed by the type II cell. The type II cell is actually somewhat resistant to hyperoxia, usually showing proliferation during prolonged exposures. Endothelial damage progresses to where capillary surface area has decreased by about 50% in some studies. The basis for endothelial cell sensitivity is not well understood.

In ARDS, the effects of oxygen can be divided into direct and indirect effects.

Indirect: CNS toxicity (seizures), sympatho-adrenal discharge, pulmonary venous hypertension, secondary infection, absorption atelectasis, surfactant inactivation and inflammation.

Direct: Can be divided into

A. Membrane damage (cells and organelles).

B. Enzyme inactivation (sulfhydryl containing enzymes)

Of the direct and indirect causes of ARDS, the direct effects are probably the most important. The biochemical events leading to these direct effects are probably initiated by free radicals generated in increased amounts because of the increased pO_2 . Among the involved oxidants: superoxide anion, hydrogen peroxide, hydroxyl radical and singlet oxygen, the hydroxyl radical (OH) is most potent, and may be responsible for much of the damage seen in pulmonary oxygen toxicity. OH is generated by the reaction of H_2O_2 and

SOA and is normally kept at very low concentrations because the protective enzymes; superoxide dismutase, catalase and glutathione peroxidase maintain the precursors at low levels. In the presence of high pO₂ the increased production of SOA and H₂O₂ probably saturates the scavenging enzymes, and results in the formation of OH. OH may then go on to cause lipid peroxidation and protein inactivation (SH crosslinking ... loss of activity) causing membrane and enzyme dysfunction, which somehow results in the syndrome of pulmonary oxygen toxicity. Other important oxidant scavengers are Vitamin E, Vitamin C, beta-carotene, and glutathione.

Indices of endothelial function.

Clearance of serotonin (5-HT) and norepinephrine (NE) from venous blood occurs to a large extent in the pulmonary microvasculature, specifically, the endothelial cells. Isolated perfused lung studies have demonstrated a significant decrease in the clearance of 5-HT after a 1 hour exposure to 4 ATA oxygen. The decrease is earlier and larger, with a slower recovery in vitamin E deficient animals. NE shows a similar pattern on exposure to oxygen. Imipramine, on the other hand, shows no change. It is cleared by a different mechanism (binding).

Prostaglandins (PG) are also metabolized to a degree in the lung, again probably the endothelial cell. In one study, a decrease in PGE₂ metabolism was noted after 36 hours of 100% oxygen. The mechanism is probably inactivation of PG dehydrogenase. Thus, a change in PG metabolism may be a relatively later event than depression of amine uptake.

Another index, possibly of both endothelial cell function and integrity, is the measurement of plasma fibronectin (FN). This is a large glycoprotein present in the plasma in large quantities (150 mg%) having diverse physiologic properties. Plasma FN has

been found to decrease under conditions of general lung damage and sepsis. A study in animals exposed to 100% normobaric oxygen demonstrated a decrease in FN at 36-48 hours, and then a dramatic increase prior to death. The decrease is believed to be the result of decreased production and/or increased clearance (RE system) whereas the preterminal increase may be due to exfoliating endothelial cells releasing ground substance into the circulation. This is only speculative as it is not certain that the FN is even coming from the pulmonary circulation, it may arise from increased production by the liver.

SUMMARY

Characterization of the ARDS syndrome of pulmonary oxygen toxicity may be possible by examining:

- 1) Pulmonary edema (CXR, diffusion capacity, etc.)
- 2) Endothelial cell function (5, HT, PGE₂, FN, NE)

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DISCUSSION

Dr. Clark opened the discussion by asking Dr. Fisher to summarize present studies of lipid peroxidation in the lung. Dr. Fisher described research in two areas: a) Tissue/blood peroxidation products: Malondialdehyde (TBA reactive material) has been shown in vitro to increase under conditions of lipid peroxidation, but studies in intact animals or with oxygen are either lacking or not promising. b) Expired gas lipid peroxidation products. M-pentane and ethane are products of lipid peroxidation and have been shown to increase in concentration in the expired gas on exposure to ozone. Again, no studies with oxygen have been performed. Additionally, some very early work with expired gas chemoluminescence (some peroxidation products are luminescent) is being done. However, substantial technical problems with both of these methods exist.

Dr. Staub asked whether the decrease in 5-HT uptake could be due to increased capillary surface area rather than endothelial cell dysfunction, and also, whether blood 5-HT levels increase to correlate with the decreased clearance demonstrated in oxygen toxic animals. Dr. Fisher could not rule out the former, but noted that imipramine clearance was unaffected at a time when capillary surface area should be decreased. Additionally, he noted that at least one study has shown an increase in blood 5-HT levels on oxygen exposure.

Drs. Greene and Menkes wondered if a direct connection between pulmonary endothelial cell function and pulmonary mechanics, or possibly hemodynamics, may exist. Both Drs. Lambertsen and Fisher believed the only direct connection to be oxygen; the toxic agent, and that the effects proceed via separate mechanisms from a common subcellular insult.

Dr. Fisher, in answering a question posed by Dr. Pietra, stated that there were no tests of pulmonary epithelial cell function which would be useful in oxygen studies. Some studies have examined surfactant production as an index of Type II cell function, but changes have been variable with exposure to oxygen.

The group turned to fibronectin with Dr. Clark asking for the mechanism of the early decrease in serum levels prior to the large preterminal increase in animals exposed to oxygen. Although the answer to this question was not available, possibilities raised by Dr. Fisher and Dr. Staub were decreased production or increased removal via the reticuloendothelial system. Furthermore, it was emphasized that no human studies of fibronectin and oxygen toxicity have been done, and that measurement in studies such as that planned is recommended.

In closing this discussion, Dr. Staub offered an approach for examining endothelial cell function which does not require the invasive techniques and radioisotopes of the aforementioned assays (5-Hydroxy Tryptamine, ACE). A substance normally 100% cleared in a single pass through the pulmonary microcirculation, PGE₁, could be infused, and the effect on systemic blood pressure would then be monitored; theoretically, a decrease in systemic blood pressure would represent decreased clearance of PGE₁ by the oxygen damaged lungs.

PULMONARY OXYGEN TOXICITY IN MAN

J. M. Clark

Hyperoxia affects pulmonary function in a continuum from the earliest changes until death. Studies performed at the University of Pennsylvania Institute for Environmental Medicine several years ago examined the effect of continuous 6- to 12-hour oxygen exposures at 2 ATA on the pulmonary function of 13 healthy young men. Symptoms began with carinal irritation 3 to 6 hours into the exposure, progressing to severe coughing, substernal burning, and ultimately dyspnea even at rest in some subjects. Two subjects had nausea and vomiting, and 2 had symptomatic orthostatic hypotension. Pulmonary symptoms generally correlated in degree with pulmonary function decrements, but some subjects had severe symptoms with relatively small objective changes, while others had minimal symptoms with prominent functional decrements. Vital capacity (VC), inspiratory capacity (IC), 1-sec forced inspired volume (FIV1), and maximal inspiratory flow rate (MIFR) all were decreased immediately post-exposure. These measurements continued to decline, reaching a maximum deficit 2-4 hours after the exposure had ended. For example: the mean VC at the end of the exposure was decreased approximately 10% from pre-exposure values, and then fell to a maximum decrement of 16% a few hours later. Individual variability was noteworthy, with one subject having a 40% maximal VC drop and others with less than 10% decrements.

The VC decrement was entirely within the IC component, since expiratory reserve volume (ERV) increased significantly. The 2-stage VC was frequently greater than the normal VC maneuver, presumably due to some degree of air trapping. The normal sitting/supine VC relationship (sitting greater

than supine VC) was reversed after exposure to oxygen and did not return until 1-2 days post-exposure. Compliance and transpulmonary pressure gradient at total lung capacity were reduced after exposure to oxygen, but not markedly. Most altered pulmonary functions returned to control values in from 1-3 days post-exposure with two subjects requiring 11-12 days. This is in contrast to Caldwell's 1 ATA study where several weeks were required for complete recovery in one subject.

The mechanism of VC decrement in oxygen exposure is not well established. The decrease in compliance probably contributed, but was not large enough to account for the total decrement in VC. It is interesting to note that two subjects had a reduced inspiratory negative pressure, suggesting the possibility that reduced chest wall strength may be partially responsible for the VC drop. The role of atelectasis was probably minimal because of the hourly triplicate VC maneuvers and absence of a change in alveolar-arterial oxygen difference.

Although the alveolar-arterial oxygen gradient in 5 subjects was not altered from control values, diffusing capacity (DLCO) was significantly reduced both immediately and 12-24 hours after termination of the exposures. The pulmonary capillary blood volume was also reduced, but membrane diffusing capacity was not changed. Recovery data are not available. However, some subjects in a French series of dives (JANUS) required more than 16 days for complete reversal of an oxygen-induced Dlco decrement.

Although it was impossible to examine the lungs of the above subjects,

a recent series of monkey studies demonstrated that chronic exposure to 1 ATA oxygen produced a marked decrease in the number of Type I alveolar cells, with proliferation and hypertrophy of Type II cells. In lung samples from hospitalized patients exposed to 0.6-1.0 ATA oxygen for 1 to 13 days, electron microscopy has shown primarily a widening of the interstitial space.

There remains some question regarding the safe limit of oxygen exposure in man. In several human exposures to oxygen at 0.5 ATA or less (more than 100 subjects), no statistically significant changes in any pulmonary function parameters were found during and after exposure durations up to 14 days at 0.5 ATA and 30 days at 0.33 ATA.

SUMMARY

1. Pulmonary oxygen toxicity produced in healthy subjects is marked primarily by symptoms of tracheobronchitis and objective changes that alter inspiratory more than expiratory function.
2. Mechanisms of the pulmonary function changes remain unclear.
3. Alveolar atelectasis is not an early manifestation of pulmonary oxygen poisoning in man.

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DISCUSSION

Dr. Menkes initiated the discussion by hypothesizing that two, possibly separate, processes were occurring;

1) The decreased vital capacity--mostly an expression of a reduced total lung capacity (TLC) due to either a) pain or motivational factors (unlikely because discomfort and FVC were not correlated in any of the data), and b) increased sensitivity of airway receptors which limit inspiratory effort (possible since transpulmonary pressure is not increased and TLC is decreased).

2) The gas exchange defect occurs later, and is distinguished by decreasing diffusing capacity, increasing lung water and probably the metabolic dysfunctions addressed by Dr. Fisher.

This was not challenged except that Dr. Staub warned that the D_{lco} measurement is dependent on the TLC and should be corrected accordingly. However, agreement was not reached on this matter.

Concerning the oxygen induced tracheobronchitis, Drs. Fisher and Clark suggested that changes in

tracheobronchial clearance may be an early indication of oxygen toxicity. One recent study shows some changes only after 6 hours of 1 ATA oxygen breathing. Dr. Lambertsen stressed that relationship between these three aspects of pulmonary oxygen toxicity (tracheobronchitis, alterations in pulmonary mechanics and gas exchange defects) is not well known, either in a physiologic or rate of development sense.

Because of the carinal irritation, Dr. Eckenhoff asked if a consistent difference had been noted between the forced and non-forced expiratory spirometry. Dr. Clark claimed that no difference in their study existed, and

he restated his feeling that the tracheobronchitis is a minimal contributor to the vital capacity decrement.

Dr. Knight wondered if other studies of oxygen toxicity had noted orthostatic hypotension, as was seen in two of Dr. Clark's subjects 2-4 hours after the cessation of oxygen breathing. Dr. Greene noted that this problem was present in Hendrick's intermittent oxygen study, and Dr. Eckenhoff noted that several subjects had symptomatic orthostasis in the AIRSAT 3 experiments. The mechanism for orthostasis after oxygen exposure as a physiologic and/or toxic effect of oxygen was discussed briefly with no consensus.

HOST FACTORS DETERMINING SENSITIVITY TO PULMONARY IRRITANTS

H. A. Menkes

There is a continuum of airway reactivity between the extremes of outright asthma and normal. Host factors exist which determine the magnitude of airway reactivity. Since atropine can block the effect of sulfur dioxide on the large airways conductance in both asthmatic and normal subjects, the reactivity is probably mediated via the parasympathetics.

In addition to the magnitude, the site of reactivity is important. Airway response can be segregated into large, small and collateral by certain techniques as shown below:

AIRWAY	TEST
Large	Maximal flow at high lung volumes Large airway conductance
Small	Closing volume Flow at low lung volumes with helium Stop - flow using bronchoscopy
Collateral	Stop - flow

By looking at different sites, a sex difference in reactivity produced by cigarette smoke has been demonstrated. Female human subjects have less small airway reactivity on challenge than do matched male subjects, whereas the large airways react similarly.

The stop/flow technique, which measures flow characteristics in an isolated, obstructed portion of lung, has demonstrated an increase in collateral resistance with no change in small airway resistance on exposure to cigarette smoke, histamine or with pulmonary edema (cardiac or alloxan generated). Methacholine in solution,

however, appears to affect both the small airways and collaterals.

Collaterals again are preferentially affected by 0.1 ppm ozone except that at higher levels (2 ppm), small airways begin to become affected as well. Additionally, with the lower dose ozone, a rapid onset of tolerance is noted after 15 or 20 min. There is a long term adaptive process as well. Intermittent exposure to ozone for several days results in a reduced response to an ozone challenge. After prior exposure to ozone, sulfurdioxide or viral infections, there is evidence that airways reactivity to histamine is increased. This does not appear to be true for collaterals but probably is so for the small airways.

SUMMARY

1. Site and intensity of airway response differ depending on host factors, insult and insult history.
2. Airway reactivity is probably a nonspecific end product of multiple processes. Thus, airways that respond more to one agent will in all probability respond more to another.
3. Oxygen may act in a similar fashion to the agents discussed, in particular; ozone.

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DISCUSSION

Dr. Staub asked Dr. Menkes to clarify the anatomical nature of the collateral airways. In answer, Dr. Menkes stated that the precise anatomic correlates are not known; they are smaller than the small airways.

Dr. Menkes then asked the group if the signs and symptoms of early oxygen toxicity may have a similar cause as the airway reactivity to histamine or ozone, and whether this would be entirely different from the toxic metabolic effects later on. Although no direct answer was given to this question, it opened a discussion of the difference between oxygen and ozone toxicity. The major points raised were:

1) Ozone, being far more reactive than oxygen, produces most of its effect and damage on the tracheobroncheal tree rather than the parenchyma. 70-30% of the ozone is removed from the inspired air before it gets past the tracheal bifurcation.

2) However, ozone does reach the lung parenchyma in sufficient quantities to cause damage. Pulmonary edema, macrophage and RBS membrane damage have all been reported in ozone toxicity.

3) Ozone is probably not a good model for the study of oxygen toxicity, but lessons can be learned which are of value in the study of pulmonary oxygen toxicity.

Dr. Lambertsen closed this discussion by asking the group whether ozone contamination may have been present in previous oxygen studies, or whether any measurements of ozone in oxygen systems or hyperbaric chambers have been made. No one knew, but the consensus of opinion was that it should be measured to rule out any contributory effect of small concentrations of ozone.

THE MEASUREMENT OF PULMONARY EDEMA IN MAN

N. C. Staub

There are three general approaches available for the quantification of pulmonary extravascular water content:

1. Microvascular fluid filtration rate.

2. Extravascular water content measurement.

3. Measurement of endothelial or epithelial permeability.

1. The measurement of fluid filtration is invasive. In one recent series of studies, pulmonary lymph flow, lymph protein concentration and the lymph/plasma protein concentration ratio were determined in newborn lambs exposed to 100% oxygen at 1 ATA. The first detectable change occurred at about 48 hours and was an increase in the protein concentration of lung lymph. Lymph flow increased during the third day. All indices continued to change until the animals died between 72-96 hours. This technique is not applicable to human studies at this time.

2. Several methods exist for the measurement of lung water content.

- a. Chest Roentgenogram

This approach is inexpensive, well standardized and the equipment is readily available. But it is only semiquantitative and not very sensitive. Pulmonary edema is diagnosed reliably when extravascular lung water content is increased by about 30%. Overdiagnosis may be a problem unless control films are available. Sequential x-ray in each individual yields the highest sensitivity and accuracy.

- b. Pulmonary Function Tests

These are relatively non-specific and of low sensitivity for the detection

of pulmonary edema. Interstitial edema does not reliably change any pulmonary function test. However, if used sequentially in a single individual, progressive changes may be related to edema formation.

- c. Tissue volume measured by soluble gas uptake.

This is done by rebreathing a soluble gas (acetylene or others) and, from the extrapolated slope of the disappearance curve to zero time, the initial mass of lung tissue exposed to the soluble gas is determined. By adding other gases, lung volume, pulmonary blood flow, and diffusing capacity can be obtained in addition to the tissue volume during a single 20 second rebreathing period. It is important to subtract the pulmonary capillary blood volume from the measured tissue volume in order to obtain the extra-vascular tissue volume. Sensitivity in detecting lung water is probably better than for the chest x-ray but the reproducibility is only about plus or minus 10%.

- d. Transthoracic electrical Impedance

This technique measures changes in electrical impedance across the chest. Since most of the current traverses the chest wall and not the lung, the results have not been promising. Focused techniques have not improved the results significantly. Therefore, most investigators have abandoned this approach.

- e. Lung Density

Focused, monochromatic gamma ray sources (such as cobalt) can be used to quantify lung density at specific sites. The technique is sensitive to changes in

lung density but does not permit one to distinguish between various causes (atelectasis, edema or vascular congestion).

Another approach to measure the density of a specific small portion of lung tissue is to compare Compton scattering induced by monochromatic gamma rays. The technique is sensitive but again suffers from lack of specificity.

f. Computerized Axial Tomography

This is another radiographic density measurement that has been tested clinically. It still lacks great precision and sensitivity but may eventually be more quantitative than the chest x-ray. Unfortunately, the machinery is bulky and impractical for use in an exposure chamber.

g. Nuclear Magnetic Resonance (NMR)

This technique uses the electromagnetic properties of water molecules when subjected to an external magnetic field and radio frequency stimulation. It has the unique ability to exclude intravascular water (flowing blood) and measure only extravascular stationary water. NMR may be useful and sensitive in future studies of pulmonary edema but currently the size and cost of equipment makes it impractical for chamber use.

h. Double Indicator Dilution

Two tracers (generally radioactive) are administered intravenously, one which rapidly diffuses into the lung tissue (tritiated water), and one confined to the vascular compartment (labeled albumin). Analysis of the outflowing blood radioactivity can be made after a single pass through the lung or after multiple circulations. The technique requires venous and arterial

catheters, removes relatively large quantities of blood and is time consuming. The method is accurate for moderate to severe pulmonary edema but the chest x-ray appears to be more sensitive for minimal edema.

i. Double Indicator Dilution using heat

This is a modification of the double indicator dilution method to use more rapidly diffusible heat. It still requires venous and arterial catheters but can be done on-line and with minimal loss of blood. The technique has promise especially for generalized pulmonary edema and sequential studies. Currently there are numerous clinical evaluations in progress.

3. The measurement of endothelial or alveolar epithelial permeability has the potential of being the most sensitive and accurate approach to the measurement of alveolar-capillary injury. Three different approaches have been tried.

a) Multiple indicator dilution. Multiple tracers are administered intravenously including radioactively labeled sodium, water, urea and albumin. These are collected from arterial blood after single pass and the time-concentration relationship analyzed. The analysis is time consuming.

b) Radioactively labeled transferrin is administered intravenously and the rate of appearance of the radioactivity over the chest (reflecting the rate of protein leaking out into the lung extravascular space) is determined with a gamma counter or scintillation camera. The test requires measurements for approximately 30 minutes but is essentially non-invasive, reproducible and has a promise of great accuracy. Human studies are in progress in a number of laboratories, but the method is not generally available yet.

c) Labeled DPTA is administered by aerosol inhalation and the disappearance of radioactivity from the lungs is determined by gamma counting over the chest. This method reflects more of the permeability of the epithelial barrier than of the endothelial barrier.

These last two methods are promising in animal and preliminary human studies. In theory, the method should be much more sensitive than the chest roentgenogram. Their only fault is a lack of standardization.

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DISCUSSION

Dr. Farhi opened the discussion by pointing out that it is presently impossible to obtain acetylene which is free of the contaminants phosphene and phosgene, and that human subjects protection committees have not been approving its use, at least at SUNY, Buffalo. Although the other members of the group were unaware of this problem, Drs. Greene and Farhi noted that other

gases can be used; Freon-22 is very close in solubility to acetylene.

A discussion concerning the usefulness of the acetylene method, or lung water measurements in general, followed. The major points made were:

1. Lung water or pulmonary tissue volume measurements must be combined with a determination of pulmonary capillary blood volume so that changing intravascular volumes will not contaminate the desired interstitial compartment volume measurements.

2. Lung water content or tissue volume does not change until relatively late in animals (sheep & rabbits) exposed to 1 ATA oxygen, and thus can not be considered to be a sensitive index of the onset of pulmonary oxygen toxicity.

3. Lung water or tissue volume measurements in humans have been contradictory; some studies have shown a very early change on exposure to hyperoxia and others have been unable to demonstrate a change (oxygen doses are highly variable also).

4. An increase in lung water/tissue volume may be the earliest event which correlates with irreversibility or ARDS. However, the point of irreversibility has not been established as most animal studies are carried out to death, and human studies not carried far enough. Animal studies are needed to correlate the point of irreversibility with the measurements discussed here.

5. Pulmonary membrane permeability changes appear to occur earlier than changes in lung water, and may correlate more closely with the onset of pulmonary oxygen toxicity than any other measurement discussed thus far.

6. Any new approach to the study of pulmonary oxygen toxicity should be correlated with measures of lung water, lymph flow as well as more traditional methods.

PULMONARY OXYGEN TOXICITY IN CONSCIOUS ANIMALS

L. E. Farhi

The use of anesthetized animals yields only a limited amount of information due to the altered physiology of the anesthetized state. Therefore, only awake, unanesthetized animals are used in these studies.

After 48 hours recovery from surgical implantation of pulmonary and systemic arterial catheters, rabbits are exposed to normobaric 100% oxygen until death. Arterial and mixed venous blood gases are collected periodically. After the initial rise, the arterial oxygen tension (PaO_2) remains relatively constant (with a shunt of about 10-20%) until just prior to the animals' death, (approximately 96 hours) when it drops suddenly and dramatically. Some investigators have found a more continuous and gradual drop in the PaO_2 with time in anesthetized animals. The $PaCO_2$ in the unanesthetized rabbits remains relatively constant, going up slightly immediately prior to the animals' death.

In contrast to the rabbits, sheep appear to have a more gradual fall in PaO_2 , with a marked increase in $PaCO_2$ prior to death. It is important to note, however, that in the sheep, the PaO_2 , although decreased from initial levels, remains sufficient to maintain life, and that the mixed venous oxygen tension (PvO_2) remains constant. Arterial pH drops dramatically consistent with the elevation in the $PaCO_2$, but the base excess also drops somewhat, possibly indicating localized acidosis in spite of the constant PvO_2 .

There appears then, to be at least 3 different possibilities for the ultimate mechanism of death in animals exposed to 1 ATA O_2 .

1. Inability to shift pulmonary blood flow to ventilated portions of the

lung with the onset of pulmonary edema. (more important in the rabbit)

2. Ability to shift pulmonary blood flow, but inability to maintain sufficient ventilation to those open areas (more important in the sheep).

3. Peripheral death. i.e., the lack of perfusion (O_2) in critical peripheral vascular beds. (possibly acting in both animals)

In studies of this latter area, microsphere injected animals did not demonstrate any significantly hypoperfused areas. Slight decreases in cardiac output associated with significant increases in the perfusion of the brain, heart and kidneys were noted in the sheep. The increases in perfusion are more likely related to hypercapnia rather than hyperoxia.

In order to determine the site of the sensing mechanism responsible for this redistribution of blood flow, animals were injected with a fluorocarbon emulsion to increase the O_2 carrying capacity without altering the PaO_2 , and then exposed to 1 or 3 ATA 100% O_2 . In both cases, the PaO_2 was similar. The PvO_2 was initially much higher in the treated group, but decreased over a short period of time to match pre-exposure control values. This, combined with an increased arterial-venous pCO_2 difference, probably represents a decrease in the cardiac output with oxygen exposure. When cardiac output is plotted against time, the decrease is far more rapid in the fluorocarbon treated animals, which would seem to indicate that the sensing mechanisms are not on the arterial side, but further downstream in the gas transport system.

In addition to these studies, some experiments were performed which

examined alveolar membrane permeability at a time prior to detectable alterations in gas exchange. Three tracers of differing molecular size were instilled in an isolated portion of lung in an animal exposed to 100% O₂. At 48 hours (which is 24 hours prior to observing any defects in gas exchange) increased permeability of the alveolar barrier was noted. Electron microscopy confirmed that the tracer had traversed the alveolar epithelium and resided in the interstitium.

SUMMARY

1. Alteration in gas exchange as indicated by blood gases is a relatively late event in pulmonary oxygen toxicity.
2. The gas exchange defect is different in both scope and timing between different animals and between the awake and anesthetized state.
3. Pulmonary membrane permeability alterations are detectable at least 24 hours prior to changes in gas exchange.

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DISCUSSION

Dr. Menkes asked Dr. Farhi if he had any thoughts on the mechanism for the relatively sudden rise in pCO₂ in the oxygen poisoned sheep. This question launched the group into a discussion of ventilatory mechanics and gas exchange, the major points being:

1) The mechanism for the rise in PaCO₂ is probably mixed: edema, small airway collapse, fluid filled alveoli, circulatory changes (both systemic and pulmonary), and probably occurs in a continuous, gradual fashion, despite the apparent "sudden" increase in pCO₂ seen in sheep.

2) Exactly what occurs at the critical point, ie, where the rate of rise in the PaCO₂ becomes much greater, is not well defined, but apparently represents a loss of the ability to compensate for the above mechanisms. There is some evidence against it being ventilatory muscle exhaustion, as no change in ventilatory muscle perfusion has been noted in Farhi's studies.

3. Absorption atelectasis is probably of minor importance in the

a. Forced expiratory/inspiratory spirometry has been shown to change, and correlation with newer tests would be desirable.

b. Although some closing volume measurements have been made in humans exposed to oxygen, helium forced spirometry has not.

c. Lung volumes and compliance have been shown to change only minimally in previous human oxygen studies.

d. The diffusion capacity is important as evidence exists which suggests a very slow recovery of the Dlco.

Mr. Dougherty wondered whether the number of repetitions of the forced expiratory maneuver at each sampling period was of importance. The group agreed that, since atelectasis is of little concern in a hyperbaric air study, the usual 2-3 repetitions are sufficient. Pertinent here also, the group believed that the spirometry should be performed every 8-12 hours at the beginning of the exposure, increasing to every 2-3 by the end of the exposure.

Dr. Staub was interested in the possibility of airway anesthesia to remove any influence of pain on the FVC. Dr. Clark and Mr. Dougherty again stated their belief that pain is a minimal contributor to the FVC decrement seen in early oxygen toxicity. Dr. Greene added that you might be removing a valuable clinical sign of toxicity by anesthetizing the large airways.

Dr. Fisher and several other members of the group were interested in the histamine challenge test and the potential application to oxygen studies. This portion of the discussion raised the following points:

a. A histamine challenge would be useful to perform pre-exposure to see if individual airway reactivity correlates with oxygen sensitivity.

b. It should also be performed during the oxygen exposures to determine if and when airway reactivity to histamine changes.

c. The test is not quantitative presently.

d. Histamine's effect lasts up to 2 hours in the asthmatic patient, and 30 minutes in the normal subject, but the effect may be reversed with aerosolized isoproterenol.

Dr. Eckenhoff reminded the group that if the pre-dive histamine challenge identifies subjects with an asthmatic diathesis, there was a possibility that those subjects would not be allowed to undergo hyperbaric exposure, as asthma is absolutely disqualifying for diving duty in the U.S. Navy. Dr. Menkes responded by stressing that a response to the histamine challenge test cannot yet be related pathognomically with the asthmatic syndrome.

Lung Water - N. C. Staub

Serial chest x-rays should be done, not only before and after the exposure but at about 12-hour intervals while the subjects are in the chamber. The x-ray could probably be taken through a chamber port with only the x-ray film plate inside. The x-ray should be read by a qualified radiologist in a single blind procedure.

Determination of lung water by the acetylene method is reasonably non-invasive and simple. But contamination by phosgene may render it unsuitable for chamber studies. The phosgene hazard is made worse by the increased partial pressure of oxygen in the chamber.

If arterial cannulations are planned for other reasons, the thermodilution technique is feasible. It is fast, relatively safe and requires minimal additional equipment. A central venous line is required but can be placed via a peripheral vein without excessive danger or discomfort.

It is unlikely that any of the measurements of lung water content will show changes during the proposed 30-48 hour exposure period. All animal data to date show changes only after 72 hours. The measurement of endothelial permeability, however, may demonstrate changes in the time period under consideration. The logistics of these

tests are difficult. The isotopes have short half lives, some are not yet approved for human use and the scintillation camera or 3-inch crystal must be inside the chamber. It would be necessary to set up the methods and practice them. It is strongly recommended if feasible.

DISCUSSION

Dr. Lambertsen wondered whether a simpler, although less discrete method of determining pulmonary membrane permeability (either endothelial or epithelial) might be available. Dr. Staub said he knew of no additional techniques, and re-emphasized that the techniques he described are quite simple and sensitive.

Regarding the chest x-ray, Dr. Eckenhoff asked whether any studies of human pulmonary oxygen toxicity had reported pleural effusions. The consensus was that no such report has been made. Dr. Fisher, however, stated that rats exposed to high oxygen concentrations do develop pleural effusions.

Dr. Fisher emphasized that the techniques described by Dr. Staub are new and most have not been used in humans exposed to oxygen. They need to be tested in oxygen exposures at 1 ATA before they are used in the complicated environment of a hyperoxic, hyperbaric chamber.

Gas Exchange - L. E. Farhi

The two samples available for gas exchange data are arterial and venous blood. The arterial blood gives an idea of how the lungs are performing, and the venous blood about how the body tissues are performing. We will examine the measurements one by one to see what samples are justified in a study of this type.

Arterial PCO₂. This gives an indication of lung ventilatory capability. There is no evidence that PaCO₂ increases in humans exposed to oxygen, at least to the extent that human studies can be carried out, but rather many studies show only a small decrease, representing mild hyperventilation. Therefore, the interest here is minimal.

Arterial PO₂. This will give an indication of pulmonary perfusion and ventilation-perfusion characteristics (V/Q). A decrease may indicate the earliest irreversible changes in pulmonary oxygen toxicity, since the PO₂ has been shown to change only relatively late in animal studies. This is of interest, then, not only to confirm the absence of irreversibility, but also because there is evidence for changing V/Q relationships in animals exposed to oxygen.

Arterial pH. This essentially reflects the changes in arterial PCO₂ in acute exposures of this type. Interest here would be minimal.

Mixed venous PCO₂. This is generally not much different than the arterial PCO₂ in terms of magnitude or direction of change. It is possible to measure by indirect methods, but the value is questionable.

Mixed Venous PO₂. Indicates overall oxygen tension of the entire body and thereby gives information about the gas

exchange status of tissues in general. Specificity and sensitivity are low, but the measurement can be made by non-invasive indirect methods - N₂/CO₂ mixture rebreathing techniques.

Mixed venous pH. Little more information than the arterial pH. **Peripheral Venous PCO₂, PO₂ and pH.** Limited usefulness as they only indicate gas exchange in an isolated limb. Variability is generally unacceptable.

From the above then, is it worth doing an arterial puncture to obtain data about gas exchange in the proposed study? Probably not. Measurements of mixed venous PO₂ would be simple, non-invasive, and by altering the protocol slightly, could yield pulmonary blood flow, lung volume, lung tissue volume and diffusing capacity.

DISCUSSION

The use of transcutaneous oximeters was posed by Dr. Staub, but few members of the group had had experience with them under hyperbaric conditions. Mr. Messier (NSMRL) stated that there are a few laboratories investigating the use of transcutaneous oximeters under hyperbaric conditions, but that it is too early to comment on the outcome.

Dr. Fisher argued that the mixed venous PO₂ would be of very limited usefulness because any change would be a late event in pulmonary oxygen toxicity, and would only indicate grossly impaired blood delivery to the tissues - essentially cardiovascular collapse. Additionally, subjects this far into the toxic process would be physically incapable of performing the rebreathing technique. Dr. Farhi agreed that the PvO₂ should not change until relatively late, but believed that the subjects

would be able to perform the technique, and that the information on the gas exchange status, combined with the additional pulmonary information obtained, justifies doing the test.

A short discussion concerning the sampling of arterial blood followed, with the following points made:

a. Arterial blood gases are not expected to change significantly in a 48 hour, 1 ata oxygen exposure.

b. Individual arterial punctures are favored unless other studies justify an arterial catheter.

c. Blood should be analyzed at depth, in the chamber, as extrapolation curves for decompressed samples do not exist.

SUMMARY

The pulmonary toxicity of oxygen and the various ways of detecting and quantifying the associated pulmonary damage have been presented and discussed.

Despite the tremendous amount of oxygen related research being done, there has been little human data available since the work of Clark, Lambertsen, Hendricks and others of a decade ago. This is not unexpected, since much of the recent work has been directed at underlying mechanisms and pathogenesis, and of necessity must use animals. However, much of the methodology is at a stage where human measurements are indeed possible. Particular promise is evident in the determination of pulmonary membrane permeability (either epithelial or endothelial) using isotopic tracers, since changes in the permeability of this membrane appears to be a very early event in pulmonary oxygen toxicity. Additionally, pulmonary endothelial cell function, as indicated by the measurement of certain blood components, may be a very useful index since the endothelial cell is recognized to be a site of early damage in pulmonary oxygen toxicity. On the other hand, measures of lung water (x-ray absorption, indicator dilution, rebreathing soluble gases, electrical impedance) and gas exchange appear to change only very late, and thus are of limited usefulness in human studies. Nevertheless, if correlated with other indices in different experimental models, these late events could be of major importance, as they may more closely indicate stages of irreversibility than the early events mentioned above. Finally, a means of identifying and reducing individual oxygen sensitivity (possibly by quantifying and manipulating oxygen scavenging systems)

would be desirable, but does not appear to be imminent.

Old methodology must not be discarded. Although most participants of this workshop agreed that forced expiratory spirometry is not an ideal index of pulmonary oxygen toxicity, little was presented that had a clearcut advantage over it in terms of simplicity and sensitivity. Furthermore, it was interesting to note that the exact cause of the forced vital capacity decrement in experimental pulmonary oxygen toxicity remains unknown, but the possibility of neuromuscular participation remains an interesting and poorly studied area.

The need for additional information concerning the human tolerance of oxygen was readily apparent during this workshop. The importance of using data to predict human tolerance of an operational or clinical oxygen exposure was confirmed. However, much of the currently available human pulmonary oxygen toxicity information loses its predictive value in the lower oxygen levels (0.50 to 1.0 ATA), which in fact, is where most human exposures occur. This could be the result of individual variability, which would be expressed more in the low dosage range, or possibly because of a lack of data. Also, recovery from pulmonary oxygen toxicity, and points of irreversibility have not been addressed in either man or animal. The ability to determine an impending irreparable stage would be of critical importance in all types of oxygen exposures. Therefore, additional human and animal data concerning the progression and recovery from pulmonary oxygen toxicity in these low exposure ranges is sorely needed.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) As part of NSMRL's continuing research in shallow air saturation diving in support of the Navy's submarine rescue capability, several military and civilian scientists met on October 27 and 28, 1981 to discuss pulmonary oxygen toxicity and the various methods of its detection and quantification. The pathogenesis, biochemistry, and characteristics of the disease in both animals and humans were reviewed and discussed at length. Methods ranging from conventional spirometry to nuclear magnetic resonance to expired gas chemoluminescence were presented. Specific recommenda-		

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tions and limitations of the techniques were obtained concerning the application of these techniques to humans in a hyperbaric environment. The need for additional data concerning the progression and recovery from pulmonary oxygen toxicity in both man and animal was apparent during this workshop.

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